The concerns of the widely publicized increasing incidence of pancreatic cancer in the Western countries in 1970 encouraged the national institutes of the Western world to promote pancreatic cancer research and challenge the development of the pancreatic cancer model. In Japan, pancreatic cancer became a high priority of national research. Despite using various laboratory and non-laboratory animal species, the induction of pancreatic cancer turned out to be a problem. Using various potent carcinogens, the targeted species were either reluctant to provide pancreatic ductal cell cancer or developed acinar cell tumors, which were extremely rare in humans. It was fortunate that the collaboration between the national German Cancer Institute and the Eppley Institute pioneered the combination of the appropriate animal model and defined the, thus far, non-existent carcinogens that led to the induction of a hamster pancreatic cancer which was nearly identical to the human disease. The introduction of this pancreatic cancer in Syrian Golden Hamsters closely mimicking the human disease in clinical and morphological aspects surprised many researchers as this species and the effective carcinogen were missing in national and most international laboratories. Since then, the animal facilities around the world opened a space for Syrian hamster research exploded to include Anatomy, Physiology, Biology, Etiology, Histogenesis, Nutrition, Prevention and Therapy, as summarized in an eBook available online [1].

The shift from the carcinogenesis program to Molecular Biology with its vast grant support by the NIH disclosed the disadvantage of this model, namely the inability of the hamster to produce transgenic litters. With the development of transgenic mice and its vigorous support by the NIH, funding for the hamster model studies almost abruptly ended. After 2011, the transgenic mouse model dominated research on pancreatic cancer. At one point, a reviewer of my grant application on the prevention of pancreatic cancer using the hamster model rejected the application. They were questioning why I was not using the mouse model.

It was ironic that the work on Nutritional, Biological, Pathophysiological, Preventive and Therapeutic studies by highly experienced researchers was ignored. The notions that most human cancers are due to environmental causative agents and the rarity of genetically-linked pancreatic cancer in humans were disregarded. The shift in carcinogenesis studies to Molecular Biology is one of the periodical tendencies of the NIH to jump from “unfinished business” to a new, unpredictable line of a “modern”, “promising” adventure.

Indeed, exploration of the genetic disposition of any cancer is a prerequisite for the elucidation of factors leading to the activation, mutation or deletion of the gene responsible for the disease. It may also lead to ways to counter the altered gene as a therapeutic means. All of these thoughts are valid when the involvement of the genes alone was the underlying factor. However, the rarity of the genetic factor in the etiology of pancreatic cancer in humans disputes this consideration.

One of the most critical issues in pancreatic carcinogenesis was why the hamster is the only species that produces pancreatic cancer almost identical to the respective human disease. This extremely relevant question remained buried.

The time has come to critically review the advances and disadvantages of the hamster pancreatic cancer model compared to the transgenic mouse model and their clinical significance, which are the most important aspects of research.

**Biology**

*Hamster Model:* Hamster islet cells show the same spectrum of transdifferentiation as the human islets [1]. In both species, the differentiation of islet cells to various pancreatic and intestinal epithelial cells occurs *in vivo* and *in vitro*. This includes the formation of intra-insular, ductular structures, the development of tumors [1] and the presence of endocrine cells, often in an excessive number, in well-differentiated carcinomas [1].
Strikingly, the spectrum of drug metabolizing enzymes within the islet cells is similar in hamsters and humans [1].

Clinical Symptoms of Pancreatic Cancer

The induced tumors cause the most common symptoms in patients [1]. Due to the differences in the anatomic structure of the pancreas and the predominant area of cancer development, the incidence of tumors in the head region of the hamster pancreas, and consequently, the frequency of jaundice is much lower than that in humans. Otherwise, remarkably, the incidence of many of the clinical findings is consistent with those in hamsters.

Tumor Morphology

The spectrum of the benign and malignant human pancreatic cancer is nearly identical to the lesions induced in hamsters [1]. As in human cancers, most induced tumors contain various numbers of pancreatic endocrine cells and show the same variation in the morphological appearance from the well-differentiated to the anaplastic types. Remarkably, the wide spectrum of induced cancer includes tumors that are rare in humans, including squamous, adenosquamous and giant cell cancers [1]. Even tumors closely resembling pancreatoblastoma are induced in offspring of hamsters that were treated with pancreatic carcinogens during their pregnancy [1].

Tumor Biology

Antigenicity: Human and hamster pancreatic cancer share the same antigenicity as summarized [1]. The exception is CA 19-9, based on the lack of the Le^e^ gene, which is the constituent of CA 19-9. Remarkably, the incidence of the expression of these antigens is similar in human and hamster cancers. Moreover, the cellular and ultra-cellular localization of these antigens are the same in both species [1]. SDS-PAGE and Western blotting procedures using anti-A antigen revealed similar major bands in the membrane fractions of both human and hamster pancreatic cells between 97 and 200 kdalton [1]. Among human pancreatic cancer-associated antigens, B-72.3, CA 125, and 17-A were also expressed in the hamster tumors both in vivo and in vitro, in a pattern similar to that seen in human pancreatic cancer cells [1]. However, DU-PAN-2 was not a frequently expressed antigen in hamster pancreatic cancer cells.

Metabolic Abnormality

It has been established that about 60% of patients with pancreatic cancer develop altered glucose metabolism and frank Type 2 diabetes, which has been regarded as pancreatic cancer symptoms or Type 3 diabetes. As reported in a clinical study, this abnormality develops even in tumors smaller than 2 cm and presents the only clinical symptom [2].

Remarkably, glucose metabolic abnormality also develops in hamsters in association with the development of microscopic cancer [3].

Genetic Alteration of Tumors

Karyotyping of hamster pancreatic cancer cell lines was seen among several alterations, including a missing Y chromosome [1]. This is of particular interest because a missing Y chromosome is frequently absent in human pancreatic cancer as well [4, 5, 6].

Most genetic changes in human pancreatic cancer, including C-K-ras, p16^INK4a^, p15^INK4b^, DPC4/SMAD4, DCC, FHIT, RB-1, and LKB1, have also been identified in the hamster pancreatic cancer. In addition to these gene alterations, increased protein expression, such as telomerase midkin, cyclooxygenase-2 (COX-2), metalloproteinase (MMP)-2, MMP-9 and membrane type 1-MMP, are shown in SGH as in humans [1].

Although cell lines derived from the induced pancreatic cancer show the same genetic alterations, one of the malignant lines (TAKA-1+BOP) did not show the mutation of the c-Ki-ras, indicating that this mutation is not essential for some tumors [7].

Tumor Histogenesis

Comprehensive in vivo and in vitro studies using various doses of several pancreatic carcinogens along with comprehensive histological, immunohistochemical, electron microscopic, and immuno-electron microscopic examination of a large number of the lesions during cancer development revealed that the earliest neoplastic lesions develop initially within the islets and later from ductal and ductular cells [1]. The unexpected development of cancer within the islets that surprised even the founder of the model presented a controversial issue as it contradicted the generally accepted view that pancreatic ductal cells are the primary origin of cancer and demanded unequivocal proof. The respective experiments provided explicit evidence for the primary involvement of islets in induced pancreatic cancer and included the findings that any condition that destroyed or damaged the islets (high fat diet, local stimulation of islet neogenesis) enhanced pancreatic carcinogenesis and transplanted islets in the non-target tissue of the carcinogen (submandibular gland) underwent malignant transformation [1]. Moreover, the immense ability of both human and hamster islet cells to differentiate into various pancreatic and extra-pancreatic cells [1] and in vitro malignant transformation of isolated hamster islets definitely supported the claim. On the other hand, any condition that destroyed or damaged the islets inhibited or prevented cancer formation. These results soften the position of opponents, including the late Dante G. Scarpelli (chairman of the Pathology Department at Northwestern University Medical Center) and the late Patrick J. Fitzgerald (ex-chairman of Pathology at Memorial Sloan-Kettering Cancer Center) to an extent that Fitzgerald in his last atlas included a case with a cancer with a suspected origin in the islet [8]. This case also was a response to the critics that islet-pancreatic cancer is limited to the hamster pancreas. Indeed, many cases of the involvement of human islets in pancreatic
ductal tumors were demonstrated [1]. Yet another indisputable point supporting the role of islet cells in pancreatic carcinogenesis was that all virus-induced tumors unequivocally derive from islets in Guinea Fowl, the only other model of pancreatic cancer [9, 10].

Transgenic View

With the rapid shift from chemical to molecular carcinogenesis, the emergence of the transgenic mouse model, and the failure of the hamster to provide a transgenic species, it lost its place. Indeed, exploration of the genetic disposition of any cancer is a prerequisite for the elucidation of factors leading to the activation, mutation or deletion of the gene responsible for the disease. It may also lead to ways to counter the altered gene as a therapeutic means. All of these thoughts are valid when the involvement of the genes alone was the underlying factor. However, the rarity of the genetic factor in the etiology of pancreatic cancer in humans disputes this consideration.

The initial enthusiasm about the transgenic model and expected promising results, increasing problems in induction tumors comparable to that in humans in biological and clinical aspects, hampered the goal and faced serious critical view [11, 12, 13, 14]. Summing up the fundamental shortfall of the transgenic mouse model, the obstacle is that too much emphasis has been devoted to the role of altered genes. Consistently adding altered genes to produce pancreatic cancer in an extraordinarily short time that mimics the human cancer is beyond the logical consideration. The major problem that is largely ignored, even by the experienced researchers in that field, is that the species used may be less ideal as a preclinical model for pancreatic cancer. Numerous carcinogenesis experiments using a variety of chemical, viral and radiation carcinogens have shown that rats and mice, which are generally, used as the test laboratory species, are resistant to provide pancreatic ductal tumors but consistently form an acinar cell tumor, notwithstanding pointing to their genetic susceptibility to acinar cell vulnerability. In that case, forcing a species to produce tumors that they naturally are unable to produce will unequivocally lead to complex errors in DNA synthesis, as is evident by the large spectrum of errors occurring in this model. Moreover, the notion of the mouse model presumes that primary gene alteration is the ethological factor, disregarding the fact that plays a minor role in pancreatic cancer in human genetic alteration. It is remarkable that the environmental role in this disease is fully ignored.

Unfortunately, the use of the hamster model came to halt at a very critical time. The role of environmental factors, including the search for suspected carcinogens and the carcinogenic action, modifying factors, promoters and inhibitors of carcinogenesis became the foreground of the research, and the relationship between Type 2 diabetes and pancreatic cancer, assumed as the promising path for the early detection of pancreatic cancer, took center stage [1]. Even worse, studies concerned with the most relevant question as to why the hamster is the only species that produces pancreatic cancer almost identical to the respective human disease remained buried.

Clearly, the hamster model is not free of adversaries. The problem includes its unsuitability for obtaining transgenic hamsters, the requirement for the proper handling of hamsters and their nutritional constraint, and the safety conditions for the use of potent carcinogens. However, these problems are manageable, in contrast to the many shortcomings of the transgenic mice model [11, 13, 14], are manageable. Consistent induction of multiple foci of hyperplastic, pre-neoplastic and malignant lesions, and serial examination of the tissue at different intervals could provide important information on the sequential genetic and other molecular alterations of the lesions and offers an avenue for discovering biological markers at each stage of carcinogenesis. The possibilities of retrograde pancreatography, examination of bile, pancreatic juice and a variety of surgical manipulation, including whole pancreas transplantation [1], are immense and provide unique advantages to this model.

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Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

References


